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Set	Items	Description
S1	84	RAGE AND REVIEW
S2	44	S1 AND RECEPTOR
S3	1	S2 AND SPLICE
S4	1	S1 AND SPLICE
S5	1	S1 AND ALTERNATIVE
S6	686	RECEPTOR(3W)ADVANCED()GLYCATION
S7	14	S6 AND SPLICE

? t s3/7/1

3/7/1
DIALOG(R)File 5:Biosis Previews(R)

18336797 BIOSIS NO.: 200510031297
Roles of the %%%receptor%%% for advanced glycation endproducts in diabetes-induced vascular injury
AUTHOR: Yonekura Hideto (Reprint); Yamamoto Yasuhiko; Sakurai Shigeru; Watanabe Takuo; Yamamoto Hiroshi
AUTHOR ADDRESS: Kanazawa Univ, Grad Sch Med Sci, Dept Biochem and Mol Vasc Biol, Kanazawa, Ishikawa 9208640, Japan**Japan
AUTHOR E-MAIL ADDRESS: hyone@med.kanazawa-u.ac.jp
JOURNAL: Journal of Pharmacological Sciences 97 (3): p305-311 MAR 05 2005
ISSN: 1347-8613
DOCUMENT TYPE: Article; Literature Review
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Diabetic patients have shorter life span and poorer Quality of Life mainly due to diabetic vascular complications. Recent in vitro and in vivo studies have shown that advanced glycation endproducts (AGE) account for diabetic vascular complications through their engagement of the %%%receptor%%% for AGE (%%%RAGE%%%). In this %%%review%%%, we summarize our recent studies on the roles of the AGE-%%%RAGE%%% system in diabetes-induced vascular injury. In vitro experiments showed that AGE engagement of PAGE leads to changes in endothelial cells (EC) and pericytes, which are characteristic of diabetic microangiopathy. Diabetic %%%RAGE%%% transgenic mice that overexpress %%%RAGE%%% in vascular cells exhibited the exacerbation of the indices of nephropathy and retinopathy, and this was prevented by the inhibition of AGE formation. %%%RAGE%%% overexpression also caused calcium handling impairment in cardiac myocytes. In contrast to the %%%RAGE%%%-overexpressing mice, diabetic %%%RAGE%%% knockout mice showed marked improvement of nephropathy. We found that human vascular cells express a novel %%%splice%%% variant coding for a soluble %%%RAGE%%% protein and named it endogenous secretory %%%RAGE%%% (esRAGE). The esRAGE neutralizes AGE actions on EC and is present in human sera. Individual variations in circulating esRAGE could be a determinant for individual differences in susceptibility or

resistance to the development of diabetic vascular complications. The AGE-%%%RAGE%%% system should be, therefore, a candidate molecular target for overcoming diabetic vascular complications.

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4/7/1
DIALOG(R)File 5:Biosis Previews(R)

18336797 BIOSIS NO.: 200510031297
Roles of the receptor for advanced glycation endproducts in diabetes-induced vascular injury
AUTHOR: Yonekura Hideto (Reprint); Yamamoto Yasuhiko; Sakurai Shigeru; Watanabe Takuo; Yamamoto Hiroshi
AUTHOR ADDRESS: Kanazawa Univ, Grad Sch Med Sci, Dept Biochem and Mol Vasc Biol, Kanazawa, Ishikawa 9208640, Japan**Japan
AUTHOR E-MAIL ADDRESS: hyone@med.kanazawa-u.ac.jp
JOURNAL: Journal of Pharmacological Sciences 97 (3): p305-311 MAR 05 2005
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DOCUMENT TYPE: Article; Literature Review
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Diabetic patients have shorter life span and poorer Quality of Life mainly due to diabetic vascular complications. Recent in vitro and in vivo studies have shown that advanced glycation endproducts (AGE) account for diabetic vascular complications through their engagement of the receptor for AGE (%%%RAGE%%%). In this %%%review%%%, we summarize our recent studies on the roles of the AGE-%%%RAGE%%% system in diabetes-induced vascular injury. In vitro experiments showed that AGE engagement of PAGE leads to changes in endothelial cells (EC) and pericytes, which are characteristic of diabetic microangiopathy. Diabetic %%%RAGE%%% transgenic mice that overexpress %%%RAGE%%% in vascular cells exhibited the exacerbation of the indices of nephropathy and retinopathy, and this was prevented by the inhibition of AGE formation. %%%RAGE%%% overexpression also caused calcium handling impairment in cardiac myocytes. In contrast to the %%%RAGE%%%-overexpressing mice, diabetic %%%RAGE%%% knockout mice showed marked improvement of nephropathy. We found that human vascular cells express a novel %%%splice%%% variant coding for a soluble %%%RAGE%%% protein and named it endogenous secretory %%%RAGE%%% (esRAGE). The esRAGE neutralizes AGE actions on EC and is present in human sera. Individual variations in circulating esRAGE could be a determinant for individual differences in susceptibility or resistance to the development of diabetic vascular complications. The AGE-%%%RAGE%%% system should be, therefore, a candidate molecular target for overcoming diabetic vascular complications.

? t s7/7/1-14

7/7/1
DIALOG(R)File 5:Biosis Previews(R)

0019461037 BIOSIS NO.: 200700120778

Lentivirus gene transfer of the endogenous circulating RAGE %%%splice%%% form blocks mechanisms leading to atherosclerosis
AUTHOR: Hudson Barry I (Reprint); Harja Evis; Arriero Maria; Nikolla Zana; Schmidt Anna Marie
AUTHOR ADDRESS: Columbia Univ, New York, NY 10027 USA**USA
JOURNAL: Circulation 114 (18, Suppl. S): p25-26 OCT 31 2006 2006
CONFERENCE/MEETING: 79th Annual Scientific Session of the American-Heart-Association Chicago, IL, USA November 12 -15, 2006; 20061112
SPONSOR: Amer Heart Assoc
ISSN: 0009-7322
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The %%%Receptor%%% for %%%Advanced%%% %%%Glycation%%% End-products (RAGE) is a strong candidate gene for the development of atherosclerosis. We have previously shown that pharmacological blockade of RAGE (recombinant soluble RAGE) or genetic deletion of RAGE suppresses the development of vascular disease in animal models. Further, in human subjects the endogenous circulating levels of RAGE are lower in plasma of subjects with coronary artery disease, suggesting an innate protective role for circulating soluble (s)RAGE. Characterization of cardiovascular tissue and cells by RT-PCR revealed the presence of RAGE and the production of sRAGE by alternative splicing resulting from inclusion of intron 9 (RAGEint9) in normal human heart and in endothelial (EC), aortic smooth muscle (AoSMC) and monocyte/macrophage (MP) cells. Using an antibody generated against the unique C-terminus protein %%%splice%%% region of RAGEint9, we detected RAGEint9 in lysates and cultured media from EC, aortic (Ao) SMC and macrophages. Transfection of RAGEint9 suppressed RAGE-ligand S100B-stimulation of MMP-9 activity and levels by similar to 2-3 and similar to 3-4-fold respectively, compared to wild-type RAGE expressing cells ($p < 0.0001$). Upon S100B incubation, RAGEint9- vs. RAGE expressing cells generated significantly decreased levels of IL-6 in the supernatant (similar to 1.6-fold; $p < 0.0001$). We generated lentiviral constructs to enable gene transfer of RAGEint9 into primary human aortic SMCs and ECs. Lentivirus transduction of RAGEint9 into human AoSMCs, reduced S100B-stimulated levels of MCP-1 by similar to 2-fold compared to cells expressing full-length RAGE ($p < 0.05$). Further, the migration of AoSMCs was blocked in RAGEint9 transduced cells in response to RAGE ligand stimulation. Finally, in ECs transduced with RAGE / RAGEint9 lentivirus, permeability assays were performed. The gene transfer of RAGEint9 into ECs blocked RAGE-ligand dependent endothelial permeability by 50%, $p < 0.001$, the hallmark of atherosclerosis. We conclude that RAGEint9 gene therapy or endogenous stimulated expression may represent a novel therapeutic modality to enhance protection against atherosclerotic disease.

7/7/2
DIALOG(R)File 5:Biosis Previews(R)

0019458768 BIOSIS NO.: 200700118509
Endogenous secretory %%%receptor%%% for %%%advanced%%% %%%glycation%%% end products in non-small cell lung carcinoma
AUTHOR: Kobayashi Seiichi; Kubo Hiroshi (Reprint); Suzuki Takashi; Ishizawa

Kota; Yamada Mitsuhiro; He Mei; Yamamoto Yasuhiko; Yamamoto Hiroshi; Sasano Hironobu; Sasaki Hidetada; Suzuki Satoshi
AUTHOR ADDRESS: Tohoku Univ, Sch Med, Dept Geriatr and Resp Med, 1-1 Seiryomachi, Sendai, Miyagi 9808574, Japan**Japan
AUTHOR E-MAIL ADDRESS: hkubo@geriat.med.tohoku.ac.jp
JOURNAL: American Journal of Respiratory and Critical Care Medicine 175 (2): p184-189 JAN 15 2007 2007
ISSN: 1073-449X
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Rationale: The %%%receptor%%% for %%%advanced%%% %%%glycation%%% end products is a multiligand receptor that plays an important role in regulating the invasiveness and metastatic potential of cancer cells. A recently discovered novel %%%splice%%% variant, the endogenous secretary %%%receptor%%% for %%%advanced%%% %%%glycation%%% end products, mediates the %%%receptor%%% for %%%advanced%%% %%%glycation%%% end-product-associated cell responses by functioning as a decoy receptor.Objectives: To evaluate the expression pattern of endogenous secretory %%%receptor%%% for %%%advanced%%% %%%glycation%%% end products in non-small cell lung carcinoma, and analyze its impact on prognosis.Methods: We performed immunohistochemical evaluation in 182 non-small cell lung carcinoma surgical specimens. The effect of an overexpressed receptor in cancer cell proliferation was also evaluated.Measurements and Main Results: The endogenous secretary %%%receptor%%% for %%%advanced%%% %%%glycation%%% end-product expression in cytoplasm was reduced or absent in 137 of the 182 (75%) carcinomas in contrast to normal lung tissues. mRNA expression was also suppressed in cancer cells. Overexpression of the secretory receptor in lung cancer cell lines had an inhibitory effect on cell proliferation, suggesting the reduced receptor expression accelerated tumor growth. Among patients with low expression of the cytoplasmic secretory receptor, the overall survival rate was significantly lower than that of patients with normal expression ($p = 0.0003$). This association was most prominent in TNM stage I patients ($p = 0.0001$). In a multivariate analysis, endogenous secretary receptor immunoreactivity was an independent prognostic factor with a relative risk of 3.1.Conclusions: The cytoplasmic endogenous secretary %%%receptor%%% for %%%advanced%%% %%%glycation%%% end-product expression has the potential to be a prognostic factor for predicting the outcome of curative surgery in patients with non-small cell lung carcinoma.

7/7/3
DIALOG(R)File 5:Biosis Previews(R)

19065460 BIOSIS NO.: 200600410855
Identification of mouse orthologue of endogenous secretory %%%receptor%%% for %%%advanced%%% %%%glycation%%% end-products: structure, function and expression
AUTHOR: Harashima Ai; Yamamoto Yasuhiko (Reprint); Cheng Chunmei; Tsuneyama Koichi; Myint Khin Mar; Takeuchi Akihiko; Yoshimura Kazunobu; Li Hui; Watanabe Takuo; Takasawa Shin; Okamoto Hiroshi; Yonekura Hideto; Yamamoto Hiroshi
AUTHOR ADDRESS: Kanazawa Univ, Grad Sch Med Sci, Dept Biochem and Mol Vasc Biol, Kanazawa, Ishikawa 9208640, Japan**Japan

AUTHOR E-MAIL ADDRESS: yasuyama@med.kanazavva-u.ac.jp
JOURNAL: Biochemical Journal 396 (Part 1): p109-115 MAY 15 2006 2006
ISSN: 0264-6021
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The cell-surface RAGE [%%%receptor%%% for AGE (%%%advanced%%% %%%glycation%%% end-products)] is associated with the development of diabetic vascular complications, neurodegenerative disorders and inflammation. Recently, we isolated a human RAGE %%%splice%%% variant, which can work as a decoy receptor for RAGE ligands, and named it esRAGE (endogenous secretory RAGE). In the present study, we have isolated the murine equivalent of esRAGE from brain polysomal poly(A)(+) (polyadenylated) RNA by RT (reverse transcription)-PCR cloning. The mRNA was generated by alternative splicing, and it encoded a 334-amino-acid protein with a signal sequence, but lacking the transmembrane domain. A transfection experiment revealed that the mRNA was actually translated as deduced to yield the secretory protein working as a decoy in AGE-induced NF-kappa B (nuclear factor kappa B) activation. RT-PCR and immunoblotting detected esRAGE mRNA and protein in the brain, lung, kidney and small intestine of wild-type mice, but not of RAGE-null mice. The esRAGE expression was increased in the kidney of diabetic wild-type mice. The present study has thus provided an animal orthologue of esRAGE for clarification of its roles in health and disease.

7/7/4
DIALOG(R)File 5:Biosis Previews(R)

18991676 BIOSIS NO.: 200600337071
Alternative splicing of the RAGE gene: Analysis and characterization in humans and mice
AUTHOR: Hudson Barry Ian (Reprint); Arriero Maria; Yang Hojin; Moser Bernhard; Harja Evis; Schmidt Ann Marie
AUTHOR ADDRESS: Columbia Univ, New York, NY 10032 USA**USA
JOURNAL: FASEB Journal 20 (5, Part 2): pA1081 MAR 7 2006 2006
CONFERENCE/MEETING: Experimental Biology 2006 Meeting San Francisco, CA, USA April 01 -05, 2006; 20060401
SPONSOR: Amer Assoc Anatomists
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Amer Soc Investigat Pathol
Amer Soc Nutr
Amer Soc Pharmacol & Expt Therapeut
ISSN: 0892-6638
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The alternative splicing of pre-mRNAs is a critical mechanism in genomic complexity, disease, and development. Studies on the %%%Receptor%%% for %%%Advanced%%% %%%Glycation%%% End-products (RAGE) indicate this gene undergoes a variety of %%%splice%%% events; however, no studies have analyzed the tissue distribution or compared evolutionary differences between species of RAGE isoforms. We recently reported on the

analysis of RAGE splicing in lung by a novel method we termed the Rapid Identification, Characterization and Expression of %%%Splice%%% forms (RICE-%%%SPLICE%%%). We applied this method to cDNA from multiple human and mouse tissue extracts for RAGE including lung, heart, brain, kidney, pancreas and placenta and compared the %%%splice%%% forms found between these two species. In humans, numerous %%%splice%%% variants were identified ranging from deletion of multiple exons (entire or in part) and intronic inclusions. These variants were predicted to change the structure and function of RAGE since they resulted in alterations in the ligand-binding domain, extensive removal of the extracellular region, production of novel proteins, and the production of soluble forms lacking the transmembrane region. In contrast, in mice, fewer %%%splice%%% variants were identified, mainly resulting in forms lacking the transmembrane region. Comparison of %%%splice%%% variants between humans and mice revealed homologous regions in the RAGE gene which undergo splicing and similar %%%splice%%% forms. Further analysis of these forms revealed the biological significance of the conserved %%%splice%%% variants. In conclusion, we have identified differences in the tissue and cross-species distribution of RAGE %%%splice%%% forms which further expands the biological repertoire of this receptor in health and disease.

7/7/5
DIALOG(R)File 5:Biosis Previews(R)

18679332 BIOSIS NO.: 200600024727
%%%Receptor%%% for %%%advanced%%% %%%glycation%%% end products is a promising target of diabetic nephropathy
BOOK TITLE: Annals of the New York Academy of Sciences
AUTHOR: Yamamoto Yasuhiko; Doi Toshio; Kato Ichiro; Shinohara Harumichi; Sakurai Shigeru; Yonekura Hideto; Watanabe Takuo; Myint Kihn Mar; Harashima Ai; Takeuchi Masayoshi; Takasawa Shin; Okamoto Hiroshi; Hashimoto Noriyoshi; Asano Masahide; Yamamoto Hiroshi (Reprint)
BOOK AUTHOR/EDITOR: Baynes JW (Editor); Monnier VM (Editor); Ames JM (Editor); Thorpe SR (Editor)
AUTHOR ADDRESS: Kanazawa Univ, Grad Sch Med Sci, Dept Biochem and Mol Vasc Biol, 13-1 Takara Machi, Kanazawa, Ishikawa 9208640, Japan**Japan
AUTHOR E-MAIL ADDRESS: yamamoto@med.kanazawa-u.ac.jp
SERIES TITLE: ANNALS OF THE NEW YORK ACADEMY OF SCIENCES 1043 p562-566 2005
BOOK PUBLISHER: NEW YORK ACAD SCIENCES, 2 EAST 63RD ST, NEW YORK, NY 10021 USA
CONFERENCE/MEETING: 8th International Symposium on the Maillard Reaction Charleston, SC, USA August 29 -September 01, 2004; 20040829
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UNILEVER
ISSN: 0077-8923_(print) ISBN: 1-57331-531-1 (H)
DOCUMENT TYPE: Book Chapter; Meeting
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Advanced glycation end products (AGEs) and the receptor for AGE (RAGE) interactions have been implicated in the development of diabetic vascular complications, which cause various disabilities and shortened life expectancy, and reduced quality of life in patients with diabetes. Diabetes-induced RAGE-overexpressing transgenic mice exhibited the exacerbation of the indices of nephropathy, and this was prevented by the inhibition of AGE formation. We also created RAGE-deficient mice by homologous recombination. They showed marked amelioration of diabetic nephropathy as compared with wild-type mice. Through an analysis of vascular polysomal poly(A)(+) RNA, we identified a novel %%%splice%%% variant coding for a soluble RAGE protein and named it endogenous secretory RAGE (esRAGE). esRAGE was able to protect AGE-induced vascular cell injuries as a decoy receptor and was actually detected in human circulation. We conclude that RAGE plays an active role in the development of diabetic vascular complications, especially nephropathy, and is a promising target for overcoming this disease. The esRAGE, an endogenous decoy receptor, may be related to individual variations in resistance to the development of diabetic vascular complications.

7/7/6

18648479 BIOSIS NO.: 200510342979
Expression profiling of endogenous secretory %%%receptor%%% for %%%advanced%%% %%%glycation%%% end products in human organs
AUTHOR: Cheng Chunmei; Tsuneyama Koichi (Reprint); Kominami Rieko; Shinohara Harumichi; Sakurai Shigeru; Yonekura Hideto; Watanabe Takuo; Takano Yasuo; Yamamoto Hiroshi; Yamamoto Yasuhiko
AUTHOR ADDRESS: Toyama Med and Pharmaceut Univ, Dept Pathol, COE Program 21, 2630 Sugitani, Toyama 9300194, Japan**Japan
AUTHOR E-MAIL ADDRESS: ktsune@ms.toyama-mpu.ac.jp; yasuyama@med.kanazawa-u.ac.jp
JOURNAL: Modern Pathology 18 (10): p1385-1396 OCT 2005 2005
ISSN: 0893-3952
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The %%%receptor%%% for %%%advanced%%% %%%glycation%%% end

products (RAGE) is a cell surface multiligand receptor of the immunoglobulin superfamily, which participates in physiological and pathological processes such as neuronal development, diabetes, inflammation, neurodegenerative disorders, and cancer. A novel %%%splice%%% variant of RAGE- endogenous secretory decoy form (esRAGE) was recently identified and is thought to be a prospective candidate to modify these RAGE- associated conditions. Here, we investigated the expression and distribution of esRAGE and RAGE proteins with domain-specific antibodies. We studied a wide variety of adult normal human preparations obtained from surgical and autopsy specimens using a tissue microarray technique. The results revealed that esRAGE was widely distributed and we classified its expression into four patterns. In pattern A, the cytoplasm is stained diffusely in neurons, vascular endothelium, pneumocytes, mesothelium, pancreatic beta cells, and macrophages/ monocytes. In pattern B, dot- like granules are stained in the supranuclear regions facing the luminal surface of the bile ducts, salivary glands, digestive tracts, renal tubules, prostate, skin, thyroid, and bronchioles. Pattern C is represented by diffuse staining in the stromal area of the arterial walls. Pattern D shows diffuse and strong staining of secreted materials such as thyroidal colloid, crystals in renal tubular lumen, and glandular lumen in prostate. This study provides, for the first time, a histopathological basis for understanding the physiological roles of esRAGE in humans, and will contribute to elucidating the participation of esRAGE in pathological processes and to exploring novel diagnostic and therapeutic concepts.

7/7/7

18631205 BIOSIS NO.: 200510325705
A novel method for the detailed analysis of gene %%%splice%%% variants
AUTHOR: Hudson Barry Ian (Reprint); Carter Angela M; Harja Evis; Arriero Maria; Yang Hojin; Moser Bernhard; Grant Peter J; Schmidt Ann Marie
AUTHOR ADDRESS: Columbia Univ, Dept Surg, New York, NY 10032 USA**USA
JOURNAL: FASEB Journal 19 (4, Suppl. S, Part 1): pA855 MAR 4 2005 2005
CONFERENCE/MEETING: Experimental Biology 2005 Meeting/35th International Congress of Physiological Sciences San Diego, CA, USA March 31 -April 06, 2005; 20050331
SPONSOR: Amer Assoc Anatomists
Amer Assoc Immunologists
Amer Physiol Soc
Amer Soc Biochem & Mol Biol
Amer Soc Investigat Pathol
Amer Soc Nutr Sci
Amer Soc Pharmacol & Expt Therapeut
Int Union Physiol Sci
ISSN: 0892-6638
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Alternative splicing of pre-mRNAs is a critical mechanism to produce a diverseproteome. Further development of methodology is needed for the thorough identification of %%%splice%%% variants produced in physiological and diseased states.The objective of this study was to

perform detailed analysis of gene %%%splice%%% variants using a novel method. As an example, we have analyzed the gene encodingthe %%%Receptor%%% for %%%Advanced%%% %%%Glycation%%% End-products (RAGE) for %%%splice%%% variants.PAGE variants were PCR-amplified from lung cDNA, cloned and analyzed by PCR-restriction digestion. Transfection of the characterized clones, into cells allowed the identification of the resulting protein. We have called this method the Rapid Identification, Characterization and Expression of %%%Splice%%% forms (RICE-%%%SPLICE%%%). Numerous %%%splice%%% variants of RAGE were identified ranging from deletion of multiple exons (entire or in part) and intronic inclusion. The variants were predicted to change the structure and function of RAGE since they resultedin alterations in the ligand-binding domain; extensive removal of the extracellular region; production of novel proteins and the production of soluble forms lacking the transmembrane region. Variants expressed in vitro were shown to produce functional proteins. Application of this method to other genes would facilitate detailed characterization of %%%splice%%% forms relevant to homeostasis and disease.

7/7/8
DIALOG(R)File 5:Biosis Previews(R)

18457565 BIOSIS NO.: 200510152065
Modulation of soluble %%%receptor%%% for %%%advanced%%% %%%glycation%%% end products by angiotensin-converting enzyme-1 inhibition in diabetic nephropathy
AUTHOR: Forbes Josephine M (Reprint); Thorpe Suzanne R; Thallas-Bonke Vicki ; Pete Josefa; Thomas Merlin C; Deemer Elizabeth R; Bassal Sahar; El-Osta Assam; Long David M; Panagiotopoulos Sianna; Jerums George; Osicka Tanya M; Cooper Mark E
AUTHOR ADDRESS: Baker Heart Res Inst, Danielle Alberti Mem Ctr Diabet Complicat, Epigenet Lab, POB 6492,St Kilda Rd, Melbourne, Vic 8008, Australia**Australia
AUTHOR E-MAIL ADDRESS: josephine.forbes@baker.edu.au
JOURNAL: Journal of the American Society of Nephrology 16 (8): p2363-2372 AUG 05 2005
ISSN: 1046-6673
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Recent studies have identified that first-line renoprotective agents that interrupt the renin-angiotensin system not only reduce BP but also can attenuate advanced glycation end product (AGE) accumulation. This study used in vitro, preclinical, and human approaches to explore the potential effects of these agents on the modulation of the receptor for AGE (RAGE). Bovine aortic endothelial cells that were exposed to the angiotensin-converting enzyme inhibitor (ACEi) ramiprilat in the presence of high glucose demonstrated a significant increase in soluble RAGE (sRAGE) secreted into the medium. In streptozotocin-induced diabetic rats, ramipril treatment (ACEi) at 3 mg/L for 24 wk reduced the accumulation of skin collagen-linked carboxymethyllysine and pentosidine, as well as circulating and renal AGE. Renal gene upregulation of total RAGE (all three %%%splice%%% variants) was observed in ACEi-treated animals. There was a specific increase in the gene expression of the %%%splice%%% variant C-truncated RAGE (sRAGE). There were also increases

in sRAGE protein identified within renal cells with ACEi treatment, which showed AGE-binding ability. This was associated with decreases in renal full-length RAGE protein from ACEi-treated rats. Decreases in plasma soluble RAGE that were significantly increased by ACEi treatment were also identified in diabetic rats. Similarly, there was a significant increase in plasma sRAGE in patients who had type 1 diabetes and were treated with the ACEi perindopril. Complexes between sRAGE and carboxymethyllysine were identified in human and rodent diabetic plasma. It is postulated that ACE inhibition reduces the accumulation of AGE in diabetes partly by increasing the production and secretion of sRAGE into plasma.

7/7/9
DIALOG(R)File 5:Biosis Previews(R)

18446161 BIOSIS NO.: 200510140661
Detection of secreted exon 8 lacking %%%splice%%% variant of %%%receptor%%% for %%%advanced%%% %%%glycation%%% end products (RAGE) from astrocytes
AUTHOR: Rouhiainen A (Reprint); Kuja-Panula J; Rauvala H
AUTHOR ADDRESS: Univ Helsinki, Ctr Neurosci, Helsinki, Finland**Finland
JOURNAL: Journal of Neurochemistry 90 (Suppl. 1): p61 AUG 04 2004
CONFERENCE/MEETING: 35th Annual Meeting of the Transactions-of-the-American-Society-for-Neurochemistry New York, NY, USA August 14 -18, 2004; 20040814
SPONSOR: Transact Amer Soc Neurochem
ISSN: 0022-3042
DOCUMENT TYPE: Meeting; Meeting Poster
RECORD TYPE: Citation
LANGUAGE: English

7/7/10
DIALOG(R)File 5:Biosis Previews(R)

18336797 BIOSIS NO.: 200510031297
Roles of the %%%receptor%%% for %%%advanced%%% %%%glycation%%% endproducts in diabetes-induced vascular injury
AUTHOR: Yonekura Hideto (Reprint); Yamamoto Yasuhiko; Sakurai Shigeru; Watanabe Takuo; Yamamoto Hiroshi
AUTHOR ADDRESS: Kanazawa Univ, Grad Sch Med Sci, Dept Biochem and Mol Vasc Biol, Kanazawa, Ishikawa 9208640, Japan**Japan
AUTHOR E-MAIL ADDRESS: hyone@med.kanazawa-u.ac.jp
JOURNAL: Journal of Pharmacological Sciences 97 (3): p305-311 MAR 05 2005
ISSN: 1347-8613
DOCUMENT TYPE: Article; Literature Review
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Diabetic patients have shorter life span and poorer Quality of Life mainly due to diabetic vascular complications. Recent in vitro and in vivo studies have shown that advanced glycation endproducts (AGE) account for diabetic vascular complications through their engagement of the receptor for AGE (RAGE). In this review, we summarize our recent studies on the roles of the AGE-RAGE system in diabetes-induced vascular

injury. In vitro experiments showed that AGE engagement of PAGE leads to changes in endothelial cells (EC) and pericytes, which are characteristic of diabetic microangiopathy. Diabetic RAGE transgenic mice that overexpress RAGE in vascular cells exhibited the exacerbation of the indices of nephropathy and retinopathy, and this was prevented by the inhibition of AGE formation. RAGE overexpression also caused calcium handling impairment in cardiac myocytes. In contrast to the RAGE-overexpressing mice, diabetic RAGE knockout mice showed marked improvement of nephropathy. We found that human vascular cells express a novel %%%splice%%% variant coding for a soluble RAGE protein and named it endogenous secretory RAGE (esRAGE). The esRAGE neutralizes AGE actions on EC and is present in human sera. Individual variations in circulating esRAGE could be a determinant for individual differences in susceptibility or resistance to the development of diabetic vascular complications. The AGE-RAGE system should be, therefore, a candidate molecular target for overcoming diabetic vascular complications.

17915973 BIOSIS NO.: 200400286730
Expression of a novel secreted %%%splice%%% variant of the %%%receptor%%% for %%%advanced%%% %%%glycation%%% end products (RAGE) in human brain astrocytes and peripheral blood mononuclear cells
AUTHOR: Youn Ju Ho (Reprint); Park In Ho; Yeon Soo In; Choi In-Hong; Shin Jeon-Soo
AUTHOR ADDRESS: Department of Microbiology, BK21 project for Medical Science, Yonsei University College of Medicine, 134 Shinchon-dong Seodaemoon-gu, Seoul, 120-752, South Korea**South Korea
AUTHOR E-MAIL ADDRESS: younjuho@korea.com
JOURNAL: FASEB Journal 18 (4-5): pAbst. 331.28 2004 2004
MEDIUM: e-file
CONFERENCE/MEETING: FASEB Meeting on Experimental Biology: Translating the Genome Washington, District of Columbia, USA April 17-21, 2004; 20040417
SPONSOR: FASEB
ISSN: 0892-6638 _(ISSN print)
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The engagement of the %%%receptor%%% for %%%advanced%%% %%%glycation%%% end products (RAGE) on the cell surface induces cellular dysfunction in a number of pathophysiological situations of vascular dysfunction, tumor cell invasion, inflammatory response, and T cell infiltration. The administration of truncated, soluble RAGE can modulate RAGE-mediated perturbations. Here, we report a novel %%%splice%%% variant (δ8-RAGE) of RAGE mRNA, which lacks exon 8 of the genomic RAGE gene and contains an early stop codon in exon 10 due to a frame shift mutation. δ8-RAGE mRNA was found in human primary astrocytes and peripheral blood mononuclear cells (PBMCs). Transient transfection experiments demonstrated that δ8-RAGE mRNA was translated into a secretory protein as deduced. Moreover, two different segments of the spliced variant were identified in PBMCs by RT-PCR. The findings of this study suggest that the diverse splicing variants of RAGE are possible in many tissues and their products may influence the RAGE-mediated

pathogenesis and immune modulation.

7/7/12
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17852045 BIOSIS NO.: 200400222100
Expression of a novel secreted %%%splice%%% variant of the %%%receptor%%% for %%%advanced%%% %%%glycation%%% end products (RAGE) in human brain astrocytes and peripheral blood mononuclear cells.
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ABSTRACT: The engagement of the %%%receptor%%% for %%%advanced%%% %%%glycation%%% end products (RAGE) on the cell surface induces cellular dysfunction in a number of pathophysiological situations of vascular dysfunction, tumor cell invasion, inflammatory response, and T cell infiltration. The administration of truncated, soluble RAGE can modulate RAGE-mediated perturbations. Here, we report a novel %%%splice%%% variant (DELTA8-RAGE) of RAGE mRNA, which lacks exon 8 of the genomic RAGE gene and contains an early stop codon in exon 10 due to a frame shift mutation. DELTA8-RAGE mRNA was found in human primary astrocytes and peripheral blood mononuclear cells (PBMCs). Transient transfection experiments demonstrated that DELTA8-RAGE mRNA was translated into a secretory protein as deduced. Moreover, two different segments of the spliced variant were identified in PBMCs by RT-PCR. The findings of this study suggest that the diverse splicing variants of RAGE are possible in many tissues and their products may influence the RAGE-mediated pathogenesis and immune modulation.

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Tissue-specific expression patterns of the RAGE receptor and its soluble forms: A result of regulated alternative splicing?
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ABSTRACT: The %%%receptor%%% for %%%advanced%%% %%%glycation%%% end products (RAGE) is known to be causally involved in a variety of pathophysiological processes, e.g. immune/inflammatory disorders, Alzheimer disease, tumors, and abnormalities associated with diabetes as arteriosclerosis or disordered wound healing. So far, human cDNAs have been characterized encoding for the RAGE receptor and a truncated soluble form lacking the transmembrane and the cytosolic domain. The latter form represents a naturally occurring competitive inhibitor of signalling pathways induced by the membrane-standing RAGE receptor. In order to perform a relative expression analysis of both RAGE forms, an RT-PCR experiment was designed allowing the simultaneous amplification of corresponding transcripts. We were able to identify three novel human RAGE transcripts all encoding truncated soluble forms of RAGE. The relative expression ratios for the full-length RAGE transcript to the sum of its %%%splice%%%-variants encoding the soluble variants varied strongly among the tissues tested. Therefore, the pre-mRNA of RAGE must be subject to regulated alternative splicing activated by extracellular cues of yet unknown cellular signalling pathways. Thus, as deduced from the occurrence at the RNA level, it can be hypothesized that there is a complex RAGE regulation network involving isoforms competing for the binding of ligands.

17238754 BIOSIS NO.: 200300197473
Novel %%%splice%%% variants of the %%%receptor%%% for %%%advanced%%% %%%glycation%%% end-products expressed in human vascular endothelial cells and pericytes, and their putative roles in diabetes-induced vascular injury.

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ABSTRACT: The binding of advanced glycation end-products (AGE) to the receptor for AGE (RAGE) is known to deteriorate various cell functions and is implicated in the pathogenesis of diabetic vascular complications. In the present study, we show that the cellular constituents of small vessels, endothelial cells (EC) and pericytes express novel %%%splice%%%

variants of RAGE mRNA coding for the isoforms that lack the N-terminal V-type immunoglobulin-like domain (N-truncated) or the C-terminal transmembrane domain (C-truncated), as well as the known full-length mRNA. The ratio of the expression of the three variants was different between EC and pericytes; the content of the C-truncated form was highest in EC, whereas the full-length form was the most abundant in pericytes. Transfection experiments with COS-7 cells demonstrated that those variant mRNAs were translated into proteins as deduced; C-truncated RAGE was efficiently secreted into the culture media, and N-truncated RAGE was located mainly on the plasma membrane. The three isoforms were also detected in primary cultured human EC and pericytes. Further, full-length and C-truncated forms of RAGE bound to an AGE-conjugated column, whereas N-truncated RAGE did not. The AGE induction of extracellular-signal-related kinase phosphorylation and vascular endothelial growth factor in EC and of the growth and cord-like structure formation of EC was abolished completely by C-truncated RAGE, indicating that this endogenous secretory receptor (endogenous secretory RAGE) is cytoprotective against AGE. The results may contribute to our understanding of the molecular basis for the diversity of cellular responses to AGE and for individual variations in the susceptibility to diabetic vascular complications.

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